UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/485,760	01/21/00	GOULMY	E 4285US

EXAMINER	
HUYNH, P	
ART UNIT	**PAPER NUMBER**
1644	10

HM12/0913

ALLEN C TURNER
TRASK BRITT & ROSSA
P O BOX 2550
SALT LAKE CITY UT 84110

DATE MAILED: 09/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/489,760	GOULMY ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

eriod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01/21/00; 6/25/01* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,9 and 20-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9 and 20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-5, 9, and 20-24 are pending.

2. Applicant's election without traverse of Group I, Claims 1-5, and 9 (now claims 1-5, 9 and 20-24), filed 6/25/01, is acknowledged.

3. Upon reconsideration, the prior art search has been extended to cover Group II that reads on the peptide of claim 1, wherein X is an arginine residue identified by SEQ ID NO: 5. Therefore, Group II, claims 1-5 and 9 are being examined along with the elected Group I, claims 1-5, 9 and 20-24.

4. The drawings, filed 1/21/00, are not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review. Appropriate action is required.

5. Preliminary Amendment to Table 1, filed 1/21/00, has not been entered. It is suggested that Applicants provide a replacement page for the revised Table 1 to include the appropriate SEQ ID NOS.

6. The International Search Reports on PTO 1449 have been considered but are crossed out because they are not appropriate for an IDS.

7. The disclosure is objected to because of the following informalities: (1) The word "INFg" on Page 21, line 23, page 28 line 27 and page 30 line 28 should be "INFγ". (2) The "TNF-a" on page 21, line 23, page 28 line 27 and page 30 line 28 should be "TNF-α"; (3) The word "IFN-a" should be "IFN-α"; (4) The word "endvolume" on page 23 line 5 is misspelled. (5) The word "b2-microglobulin" on page 25 line 4, page 30 line 34 should be "β-2-microglobulin". (6) SEQ ID NO: is required on page 25 line 1, page 31 line 2 and page 30 line 34. (7) The "(GvHD)) ." on page 1 line 12 should be "(GvHD))."". Appropriate correction is required.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-5, 9 and 20-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a peptide constituting a T-cell epitope of the minor Histocompatibility antigen HA-1 wherein the peptide consists of VLXDDLLEA (SEQ ID NO: 1), which is 9 amino acid residues in length where X represents a histidine or an arginine for diagnosing minor Histocompatibility antigen (HA-1) incompatibility between donor and recipient of bone marrow transplant using in vitro CTL assays (See pages 5, 7, 14-17, 25-26 of the ~~specification), generation of VLHDDLLEA or VLRDDLLEA~~ specific CTL *in vitro* for adoptive immunotherapy, does not reasonably provide enablement for (1) *any* immunogenic peptide "comprising" the sequence of SEQ ID NO: 1 wherein X represents a histidine or arginine; (2) *any* "derivative thereof" having similar functional or immunological properties; (3) *any* "analog thereof", *any* (4) "vaccine" or (5) *any* "pharmaceutical formulation" comprising said immunogenic polypeptide, derivative or analog thereof to prevent graft versus host disease or to treat HA-1 related autoimmune disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only two peptides of minor Histocompatibility antigen HA-1. The peptides are VLHDDLLEA (SEQ ID NO: 2) and VLRDDLLEA (SEQ ID NO: 5) wherein the peptides having a structure of nine amino acid in length for diagnosing incompatible minor Histocompatibility antigen HA-1 associated with bone marrow transplant.

The specification does not teach how to make and use *any* immunogenic peptide "comprising" the sequence of SEQ ID NO: 1 because the term "comprising" is open-ended. It expands the polypeptide to read on a full-length polypeptide or intact protein. By reciting the term "comprising" in the claims, the polypeptide encompasses indefinite number and type of additional amino acids, in addition to the amino acids which already recited in SEQ ID NO: 1.

Abbas *et al* teach that even a single amino acid differences in the peptide fails to bind to the T cell receptor or loss of T cell function or both (See page 130, Table 6-7, in particular). Likewise, even a single amino acid differences in the nanomeric peptide can have a drastic effect on binding as evidence by applicants' data (see Figure 4, in particular). Because of the indefinite number of amino acids that may be encompassed in the polypeptide of instant claims and there is no disclosure about the structure associated with functions of *any* polypeptide, it is not clear a polypeptide "comprising" SEQ ID NO: 1 would have similar functional or immunological properties as SEQ ID NO: 1.

Furthermore, there is no guidance in the specification as to which amino acid residues within the full length amino acid sequence that after substitution, deletion or insertion will retain both structure and function similar to SEQ ID NO: 1. Colman *et al* teach that even a single amino acid difference in an antigen can abolish the antibody-antigen interaction entirely (page 33, in particular). Given the lack of guidance and working examples, predicting what changes can be made to the peptide of SEQ ID NO: 1 that after substitution, deletion, insertion and/or modification will retain both structure and have "similar immunological function" is unpredictable. Since the specification fails to provide guidance regarding which amino acid can tolerate change, it follows that the "derivative" that are structurally and functionally equivalent to SEQ ID NO: 1 is not enabled. It also follows that the "analog thereof" regardless whether it is has similar or antagonistic activity is not enabled.

In addition, the specification fails to provide guidance and *in vivo* working examples as to whether a "vaccine" or a "pharmaceutical formulation" comprising the immunogenic polypeptide, derivative thereof, or analog thereof would prevent Graft versus Host disease or would be able to treat HA-1 related autoimmune disease.

By definition, a vaccine is a composition to induce a specific immunity that **prevent** or protect against a specific disease caused by a specific agent (See Fundamental Immunology, second edition, pages 987-988, in particular). One of the criteria for a vaccine is the levels of antibody (humoral immune response) before and after immunization and the success of

vaccination is judged by the extent of increase in the level of HA-1 peptide specific antibody. The second criterion for a vaccine is the ability to induce tolerance in the HA-1 negative donor and thereby protect the HA-1 positive recipient upon receiving the organ from Graft versus host disease or induction of tolerance in the HA-1 negative recipient. A vaccine and/or a "pharmaceutical formulation" in the absence of *in vivo* data is unpredictable because (1) the peptide/polypeptide may be inactivated before producing an effect due to proteolytic degradation or immunological inactivation or the inherently short half-life of the peptide/polypeptide; (2) the peptide/polypeptide may not bind to the TCR, or may not reach the target area because, i.e. the peptide/polypeptide may not be able to cross the mucosa or the peptide/polypeptide may be adsorbed by fluids, cells and tissues where the peptide/polypeptide has no effect; and (3) other functional properties, known or unknown, may make the peptide/polypeptide unsuitable for in vivo therapeutic use, i.e. such as adverse side effects which prohibit the use of the peptide for inhibiting Graft versus host disease. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Since there is no *in vivo* working examples in the specification as filed to demonstrate the effectiveness of using *any* peptide for preventing GVH, or treating HA-1 related autoimmune disease, it is not clear that a vaccine or a "pharmaceutical formulation" against Graft versus host disease treating HA-1 related autoimmune disease comprising said immunogenic peptide is enabled. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

10. Claims 1-5, 9 and 20-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification discloses only two peptides of minor Histocompatibility antigen HA-1. The peptides are VLHDDLLEA (SEQ ID NO: 2) and VLRDDLLEA (SEQ ID NO: 5) wherein

the peptides having a structure of nine amino acid in length for diagnosing incompatible minor Histocompatibility antigen HA-1 associated with bone marrow transplant.

The specification fails to disclose *any* peptide or *any* immunogenic polypeptide "comprising" the sequence VLXDDLLEA, *any* "derivative thereof", *any* "vaccine" or "formulation" comprising *any* peptide, *any* immunogenic polypeptide, *any* "analog" *any* "derivative thereof" having similar functional or immunological properties or *any* "analog wherein the analog is an antagonist". There is insufficient **written description** about the scope of each claimed genus, each of which encompasses a variety of subgenera. With the exception of peptides represented by SEQ ID NO: 2 and 5, there is no description about the structure associated with functions of *any* peptide, *any* immunogenic polypeptide, *any* "derivative thereof", *any* "analog" mentioned above. Applicants have not described the types of an amino acids (neutral, hydrophobic, hydrophilic) to be added, substituted, deleted, and/or modified to arrive at a peptide or immunogenic polypetpide "comprising" the sequence of VLXDDLLEA that has similar functional or immunological properties or antagonistic immunological properties as SEQ ID NOS: 2 and 5 to be used for any purposes, including "vaccine" or a "pharmaceutical formulation" for induction of tolerance in HA-1 negative donor or HA-1 related autoimmune disease. Furthermore, an analog or antagonist may include protein, peptide, nucleic acid, carbohydrate, or organic molecule. The specification does not indicate what the analog or antagonist is and essentially has not enabled for the breadth of the claimed invention in view of the teachings of the specification. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *see University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1, 2, 3, 4-5, 9 and 20-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "having similar functional or immunological properties" as recited in claims 1, 2 and 9 renders the claims indefinite because the metes and bounds of the specific immunological properties are not defined.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-2 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Nagase *et al* (DNA Res 3:321-329, 1996; PTO 892).

Nagase *et al* teach a peptide comprising the sequence of VLXDDLLEA wherein X is an arginine (See enclosed sequence alignment, in particular). The term "comprising" is open-ended; it expands the peptide to read on the reference polypeptide of Nagase *et al*. Further, the reference peptide is considered as a derivative of the claimed peptide wherein X is a histidine in claims 1-2 or the analog recited in claim 9. Thus, the reference teachings anticipate the claimed invention.

15. Claims 1-2, 4-5, 9, 21 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Haan *et al* (Eur J Immunol 26:2680-2685, 1996; PTO 892).

Haan *et al* teach chimpanzee HA-1 and HA-2 peptides which have the following sequence YXGEVXVSV and are 9 amino acids in length and these HA-1 and HA-2 peptides are assumed to be the derivative and analog of the claimed immunogenic polypeptide because they have similar functional or biochemical properties of the human HA-1 and HA-2 (See page 2683, column 1, paragraph 1, in particular). Claims 4-5, 21 and 23 are included in this rejection because the vaccine comprising the immunogenic polypeptide which is the derivative or analog of HA-1 and HA-2 that has the same structure and inherent immunological functional properties. Haan *et al* further teach the peptides are in HBSS buffer with 50mM Hepes (page 2682, column 1, 1st paragraph, in particular) which can be used as a pharmaceutical medium and the use of non-human primates as a model to study bone marrow transplantation-related reactivities such as

GVHD and graft-versus leukemia reactions (See page 2684, in particular). Thus, the reference teachings anticipate the claimed invention.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

18. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
September 10, 2001

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP ~~1800~~ 1640